REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully traversed.

The July 29, 2003, personal interview between Examiners Guzo and Nguyen, inventor Steven Goldman, M.D., Ph.D., and applicant's undersigned attorney is gratefully acknowledged. The substance of that interview is summarized below.

The above amendment to the specification is made so that the revised paragraph (particularly with regard to the sentence immediately after that being amended) is internally consistent.

The objection to claim 27 under 37 C.F.R. § 1.75(c) is respectfully traversed in view of the above amendments.

The rejection of claims 28-30, 33-39, and 44-46 under 35 U.S.C. § 112 (1st para.) for lack of enablement is respectfully traversed.

As demonstrated by the accompanying Second Declaration of Steven A. Goldman under 37 C.F.R. § 1.132 ("Second Goldman Declaration"), the claimed invention is highly effective in treating a neurodegenerative disease.

To test the feasibility of using brain-derived neurotrophic factor ("BDNF") contained in an adenovirus ("AdBDNF") or an adenovirus containing noggin ("AdNoggin") to induce striatal neurogenesis to treat Huntington's Disease, AdBDNF and AdNoggin were intraventricularly injected into Huntington mutant R6/2 mice and into normal wild-type mice (Second Goldman Declaration ¶4). The results are described in the Second Goldman Declaration at ¶¶ 5-10.

AdBDNF induced striatial neuronal addition in both wild-type and R6/2 mice (Second Goldman Declaration ¶ 11). Among the R6/2 mice, AdBDNF-treated animals exhibited 135.0 ± 34.1 BrdU+/βIII-tubulin+ cells/mm^3, significantly more than their counterparts given AdNull (20.1 ± 6.5) or saline (5.1 ± 7.8) ($p<0.05$ by ANOVA followed by post hoc Bonferroni t-test) (Id.). Similarly, wild-type mice injected solely with AdBDNF exhibited 84.3 ± 30.5 BrdU+/βIII-tubulin+ cells/mm^3, significantly more than mice given AdNull (13.1 ± 9.7) or saline (4.2 ± 3.0) ($p<0.01$) (Id.). Thus, AdBDNF treatment elicited substantial neuronal addition to the neostriata of both R6/2 transgenic and wild-type mice (Id.). In both, the neuronal phenotype of AdBDNF-induced BrdU+/βIII-tubulin+ cells was confirmed by immunolabeling for NeuN (Id.). In neither the R6/2 mice nor wild-types was

any evidence of striatal neurogenesis observed in saline-treated controls, at least among mice sacrificed at 10 weeks of age (Id.).

AdBDNF/AdNoggin cooperatively induced striatal neuronal recruitment (Second Goldman Declaration ¶ 12). It was found that the concurrent use of AdBDNF and AdNoggin, by effectively providing a permissive and instructive environment for striatal neurogenesis, greatly enhanced neuronal recruitment to the striatum (Id.). Wild-type ("WT") mice treated with AdBDNF/AdNoggin exhibited 219.9 ± 19.4 BrdU+/βIII-tubulin+ cells/mm^3, significantly more than AdBDNF-, AdNull- or saline injected WT mice ($p<0.01$ by ANOVA, with post hoc Bonferroni t-test) (Id.). Similarly, the neostriata of AdBDNF/AdNoggin-treated R6/2 mice harbored 277.0 ± 52.7 BrdU+/βIII-tubulin+ cells/mm^3, significantly more than observed in R6/2 mice given AdBDNF, AdNull, or saline (each $p<0.05$ by ANOVA with post hoc Bonferroni t-tests) (Id.). Thus, in both WT and R6/2 mice, BDNF and noggin acted cooperatively to induce striatal neuronal recruitment (Id.). Importantly, AdBDNF/AdNoggin treatment elicited as strong a neurogenic response in R6/2 mice as in WT mice, suggesting that neither the mutant huntingtin phenotype, nor any antecedent compensatory progenitor response, had depleted or exhausted the progenitor pool in R6/2 mice (Id.).

To demonstrate that the use of AdBDNF and AdNoggin in combination delayed functional deterioration, motor coordination and balance were measured using rotarod (Second Goldman Declaration ¶ 15).

It was found that the AdBDNF/AdNoggin-treated mice exhibited a significant deceleration in motor deterioration, relative to both their saline and AdNull-treated R6/2 controls (Second Goldman Declaration ¶ 16).

These results indicate that the concurrent overexpression of BDNF and noggin may be used to induce neuronal recruitment from endogenous progenitor cells in the R6/2 huntingtin mutant neostriatum (Second Goldman Declaration ¶ 17). When these mice were assessed at 10 weeks of age, BDNF overexpression beginning at 4 weeks was found to have induced the addition of at least 135 new neurons/mm^3 (Id.). Although significant, this represents <1% of the striatal neuronal population (Id.). On this basis, BDNF was co-expressed together with noggin to suppress non-neurogenic pathways of subependymal cell differentiation, and thereby increase the pool of progenitor cells potentially responsive to BDNF (Id.). By this means, >400 neurons/mm^3 were added to the AdBDNF/AdNoggin-treated R6/2 striatum within 6 weeks of viral injection (Id.). Rotarod testing revealed that

concurrent AdBDNF/AdNoggin treatment delayed the onset of motor deterioration in R6/2 mice, and slowed the progression of their motor deterioration, relative to AdNull- and saline-treated controls (Id.). These results further indicate that induced neurogenesis may be associated with a delay of symptom progression in a prototypic mouse model of Huntington's Disease (Id.). These results suggest that induced neurogenesis from resident progenitor cells may comprise a feasible strategy for therapeutic neuronal replacement in Huntington's Disease, and more generally, as a means of reconstituting lost multinuclear circuits in the diseased adult forebrain (Id.).

In view of the data set forth in the Second Goldman Declaration, it is submitted that the rejection under 35 U.S.C. § 112 (1st para.) for lack of enablement should be withdrawn.

The rejection of claims 1-8, 13-20, and 27 under 35 U.S.C. § 112 (1st para.) for non-enablement is respectfully traversed in view of the above amendments.

The rejection of claim 48 under 35 U.S.C. § 112 (2nd para.) for indefiniteness is respectfully traversed in view of the cancellation of this claim.

The rejection of claims 1-5, 7, 13-17, and 19 under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 6,071,889 to Weiss, et. al., ("Weiss") is respectfully traversed.

Weiss teaches a method of inducing proliferation of a multipotent neural stem cell by administering various growth factors (e.g., brain-derived neurotrophic factor) as proteins *per se* or as nucleic acids encoding such proteins. However, Weiss' approach is directed to mitotic expansion of neural stem cells rather than directing post-mitotic neuronal differentiation and migration of its progeny. Weiss fails to teach "injecting the nucleic acid construct into a subject's lateral ventricles or ventricular wall zone under conditions effective to express the neurotrophic factor and to induce addition of neurons in any one or all of the caudate nucleus and the putamen of the subject" as set forth in claim 1 and "injecting the nucleic acid construct into the subject's lateral ventricles or ventricular wall zone under conditions effective to express the neurotrophic factor and to recruit addition of neurons to any one or all of the caudate nucleus and the putamen of the subject" as set forth in claim 13. In the outstanding office action, the U.S. Patent and Trademark Office ("PTO") asserts that these features are taught by Weiss in column 50, lines 39-55 which states that administration of growth factors might cause directly infected subependymal cells to migrate out into the striatum, and hence to differentiate into neuronal cells. However, Weiss provides no evidence for what growth factors might specifically be competent to achieve this purpose, no

establishment of an appropriate means of delivery, no assessment of whether neurons or glia might be generated through this approach, no indication of what neuronal phenotypes might be induced, no specific evidence that medium spiny neurons of the caudate and putamen might be so induced, no indication of whether newly induced neurons might extend fibers to efferent targets, no indication that any such neurons so induced and integrated might assume functional competence, no means of accentuating neuronal induction via concurrent glial suppression (e.g., via noggin), no assessment of what growth factors or combinations thereof might be sufficient to achieve therapeutic endpoints, and no assessment or prediction of what appropriate disease targets for such strategies might be. Overall, Weiss fails to posit, specify or prove how growth factor addition to the adult brain might cause the specific addition of medium spiny pallidal projection neurons to the adult caudate nucleus and putamen.

Since Weiss does not provide an enabling disclosure of the present invention nor teach features being claimed, it is not anticipatory. Therefore, the rejection of claims 1-5, 7, 13-17, and 19 based on Weiss should be withdrawn.

The rejection of claims 1-4, 7, 13-16, and 19 under 35 U.S.C. §102(a) as anticipated by Benraiss, et. al., "*In Vivo* Transduction of the Adult Rat Ventricular Zone with An Adenoviral BDNF Vector Increases Neuronal Production and Recruitment to the Olfactory Bulb", Soc. Neurosci. 25: 413.3 (1999) ("Benraiss"), as evidenced by Weiss, is respectfully traversed.

Benraiss only teaches addition of neurons to the olfactory bulb. It fails to teach "addition of neurons to any one or all of the caudate nucleus and the putamen of the subject" as set forth in claim 1 and "addition of neurons to any one or all of the caudate nucleus and the putamen of the subject" as set forth in claim 13. In the outstanding office action, the PTO asserts that these features are inherently taught by Benraiss as evidenced by Weiss. However, as demonstrated *supra*, the above-identified features are not taught by Weiss. Therefore, like Weiss, Benraiss cannot anticipate the claims and the rejection under 35 U.S.C. § 102 must be withdrawn.

The rejection of claim 1, 6, 13, and 18 under 35 U.S.C. § 103 for obviousness over Weiss in view of U.S. Patent No. 5,965,440 to Reeves is respectfully traversed. Reeves is cited as teaching an inducible promoter. However, Reeves does not overcome the above-noted deficiencies of Weiss. Accordingly, the rejection based on the combination of Weiss and Reeves should be withdrawn.

In view of all the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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